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THE STRUCTURE OF PROTOPLASM[1]

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It may seem to many that there has been little progress in recent years in our conceptions as to the constitution of protoplasm. While great advances have been made in our knowledge of the molecular constitution of various proteins *in vitro*, we cannot yet feel sure of the adequacy of the data so obtained as a basis for conceptions as to the molecular constitution of substances found in the living protoplasm. Further, the discovery of such bodies as hormones, vitamines, etc., with their far-reaching physiological significance is after all largely a matter of qualitative observations which have not yet been brought into relation with our knowledge of the visible protoplasmic cell structures. And yet it seems to me that the new data on the chemistry of the colloids and the results of experimental studies in genetics, as well as the more direct observations of cytologists, have been producing some very fundamental changes in our conceptions as to the chemical and physical characteristics of the cell and protoplasm.

I have no new theory of cell organization to propose, but desire to bring together the data from cytology, colloid chemistry, and genetics which bear on this, for all biologists, fundamental problem. That the organization of the cell is the fundamental problem of all biology was never clearer than it is to-day. The theory that all organisms are constituted of cells, each with its own more or less subordinated life history, and that the functions of all organs, tissues, etc., are in the last analysis the functions of cells, has proved the most illuminating, the most universal in its application, of any viewpoint ever developed in the history of biology. It is so familiar, so much a commonplace of all thought and speculation that it seems idle to dwell upon it, and yet it is certainly a unique situation in science that practically the whole developmental series of both plants and animals are *cellular* in organization. A structure so complex as the *cell* must have had an evolutionary history, but the whole evolution of living organisms as we know them is the history of the increasing specialization of structure and corresponding division of labor between cells whose fundamental architecture remains the same.

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[1] Address of the retiring president of the Botanical Society of America, delivered at Pittsburgh, December 31, 1917.

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The cell theory that higher organisms are complexes of simpler organisms which by their manifold interactions build a more differentiated organic unit was never more firmly established, more thoroughly in harmony with all known facts, than it is to-day. Opponents there are of this doctrine, but even they admit that the great problem to be solved is the discovery of the organization of protoplasm, and this search to discover the real structure of the protoplasm is the goal of all cell studies. There is no real diversity of opinion between biologists as to the significance, the methods, and the goal of cytological investigation. The viewpoint which I wish to emphasize is that the structure of protoplasm is the structure of the cell. The search for some ultra-microscopic structure of living substance as such and more deep-seated than cell structure, has, so far, proved as vain as the older attempts to demonstrate the existence of a vital force.

To the theoretical biologist the biological sciences, old and new, anatomy, surgery, physiology, pharmacology, pathology, bacteriology, and genetics—these great fields of human thought and effort which have borne fruits of such inestimable value for civilization and the progress of the human race are all of interest as they contribute to the explanation of the cell structure and its functions, for to-day no really critical student of biology questions that in the organization of the cell lies the world-old riddle as to the nature of life, its origin, possibilities, and limitations.

The cell theory with its varied implications lies at the center of all biological thought and interest, and the history of the cell theory has been a continual vindication of the methods of observation and analysis as against the loose and easy methods of *a priori* speculation. No philosopher ever guessed that life units as we know them arise only by division, that the fertilization of the egg is the fusion of cells, or that heredity is based on a painstakingly equal division of a germ plasm. Whatever we may believe about pre-established harmonies in the organization of the universe, it is obvious that our minds are not so constituted that it is easy for us to guess the truth or that whatever is true about the cell seems natural and to be expected. The great discoveries of biology have been reached by the laborious and sometimes seemingly almost blind method of trial and error, with error always largely in evidence.

We are inclined to speak of the present as a period of criticism and of the application of fundamental discoveries of science to practical affairs, but it seems to me equally obvious that, as noted, the new data in chemistry as well as from experimental breeding and cytology are gradually and sometimes perhaps almost subconsciously changing our viewpoints as to many of the old conceptions of life and protoplasm. We can perhaps, as I have suggested above, classify in three groups the movements and discoveries which are influencing our conceptions of life structures and life processes. I shall speak of the contributions of cytology, of the chemistry of the colloids, and of genetics to our conceptions of protoplasm.

DATA FROM CYTOLOGY

In considering the modern cytological viewpoint as to the structure of the cell, I may first indicate the general sense in which I shall use the terms relating to the cell and its parts. And I must state at once that nothing is further from my intention than to attempt to provide a series of hard and fast definitions of structures as fluctuating and plastic as are the cell and the materials of which it is composed. A word is perhaps necessary here as to the place of definitions in modern science. It is frequently stated that science progresses with the increasing clearness of our definitions, and that much useless controversy would be avoided if contestants were compelled to define their terms. It seems to me that in these statements modern science is accepting and perpetuating a mediaeval dogma which since Darwin has practically lost its significance. In the days of metaphysics and the use of the deductive method in logic, it was of vast importance to know just how much was implied in any term used in a major premise, for on that and that alone depended how much could be gotten out of it in conclusions. Especially when certain conceptions or ideas were assumed to be self-evident or axiomatic, it was vital to know just how much was implied in a given term as self-evident. With modern science, so-called axioms as relating to any matters of scientific importance have largely gone the way of all the earth. With a realization of the supremacy of the inductive method we become less restrictive in our use of terms in our larger interest as to what is really true of the subjects to which they relate. Relatively few modern controversies are due to misunderstanding of each other by the principals. In the dispute between Weismann and Spencer over the inheritance of acquired characters it was no mere matter of terms, and in the flare-up over the meaning of the word *genotype* which followed the visit of Johannsen to this country the obscurity was all in the facts about the constitution of the germ plasm rather than in the various definitions and usages proposed for the term. There is a positive danger in the use of definitions which is obvious in the discussion of the factorial hypothesis raging just now. There is a group of geneticists who would frame a definition of the term *unit factor* so very broad and so empty of all concrete and specific implications that it would become an abstraction like many of the conceptions of mathematics. This is the aim of those who would make Mendelism a system of notation. A mere one factor conjugated with one factor makes two factors, and one factor separated from the other factor gives two independent factors. Representatives of these tendencies sometimes try to win support by accusing their opponents of ignorance that one and one make two and one from two leaves one. No one disputes such mathematical obviousness, but it is the death of science when concrete realities are attenuated to fit such empty generalizations. It is of the very essence of modern scientific method and spirit that it has broken away from such formalism and resists the temptation of the human mind to accept and remain content with such empty formulae. It is a familiar fact to critics of literature and art as well as to scientists that every great advance in knowledge with new concrete discoveries and every great creative age is followed by a period when the new data, instead of being made the basis for further advances, become the shibboleths of new schools. Concepts that have been fruitful and actually represent a great advance in knowledge come to be used in a mystical, absolute, and all-embracing sense quite unimplied in their original usage.

We may return from this brief disquisition on definitions and terminology to our theme with an illustration of this misuse of terms. The term *protoplasm* as used by Purkinje was merely descriptive and concrete in its reference to the material of young embryos. Von Mohl made it more definite and still more specific as the term applied to the slimy viscid material which makes up the content of the cell inside the cell wall, which latter structure to him was still a very important if not essential element in his conception of the cell. He was also still far from free of mystical conceptions as to the nature of life and life-processes as something quite outside of and beyond the properties of protoplasm. Huxley made protoplasm the physical basis of life, a conception which still allowed for much play of the imagination as to the existence of forces and principles which could be imagined, as Bergson imagined them, to use the protoplasm as the mere physical substratum for the manifestation of their autonomous activities. In the elimination from modern biology of mystical conceptions as to vital force or forces in a super-physical realm we have come, however, to transfer a certain element of mysticism to the conception *protoplasm* itself, and to refer to the properties of protoplasm in quite the same fashion as the mediaevalists did to vital force, formative principles, etc. We say or obviously imply too easily, especially to our elementary students, that all the functions of life in plants and animals are explainable as due to the properties of protoplasm to assimilate, grow, divide, etc. Such statements are true so far as we know, but they are so general, so empty of all concrete specification as to the facts of assimilation, growth, and reproduction, that they are mere formalisms quite as deadening in the end to the real progress of research and discovery as were the conceptions of the "vital spirits" of mediaeval physiology in their relations to the functions of nerves, muscles, etc., or the nutrient, reproductive, sentient, etc. soul powers of Aristotle—conceptions which when accepted as finalities tended to discourage rather than to stimulate research. In stating, then, that I shall use the term *protoplasm* as referring broadly to the whole sum of materials which make up the cell, including the cell wall, metaplasm, starch, fat, cell sap, even inorganic crystals and water of inclusion, nothing is farther from my intention than to give a definition of protoplasm. Protoplasm is in most intimate relations of interchange with its environment, and, further, there is surely no hard and fast line between its external environment and its so-called internal environment, using the latter term to refer, for example, to foods and wastes dissolved in the vacuolar cell sap.

With this understanding as to definitions, I shall use the word *cell* as referring to the whole protoplasmic life unit, including the wall or envelopes of every kind. This will include in the cell conception multinucleated coenocytes and plasmodia as well, though it is obvious that here the content of the term is stretched until its usefulness becomes impaired. Still, I may note without discussion that this, in my opinion, is much better than to regard coenocytes and plasmodia as non-cellular or as tissues with cell walls omitted, as many do. We have here a case of which there are so many, where nature simply mocks our categories and shows the weakness of attempts to separate by definition objects that are so intimately connected in their evolutionary history.

If, as I have suggested above, the visible organization, its architecture, is the structure of the protoplasm, we are confronted with the further significant consideration, which the numerous studies on the algae, fungi, and all the invertebrate phyla which have appeared in the last two decades have brought out very clearly, that this organization of the cell is everywhere broadly speaking the same. From the one-celled alga or fungus to the highest plant or animal, the differentiation of nucleus, cytoplasm, chromosomes, spindle fibers, etc., is everywhere present, and in their general nature and functions and in their essential interrelations these structures are the same. I am not overlooking the fact that nuclei have not been satisfactorily proved to exist in the bacteria, or that the central body of the blue green algae can perhaps best be considered as only a very aberrant form of nucleus. The macro- and micro-nuclei of the infusoria also imply a quite different type of organization from that of the common uninucleated cell. We must not, however, allow ourselves to be blinded by these facts, significant as they are and fruitful as they may become in deepening our conceptions of cell organization, to the great outstanding fact that evolution as we know it has not consisted in the production of new types of protoplasmic structure or cellular organization, but in the development of constantly greater specialization and division of labor between larger and larger groups of cells. The obviousness of this fact is brought out most conspicuously by the diagrams of a typical cell. Whether taken from the text-books of botany or zoology, these schematic figures all show a striking agreement as to the more fundamental structural features of a so-called typical cell. The differences between plants and animals, or between Pleurococcus and the pine, are not indicated primarily in the general organization of their cells.

We shall see most clearly the difference between the former and the new viewpoints when we note the disappearance of the old corpuscular theories of protoplasmic structure from the literature of present-day cytology. To explain certain evidences of the transmission of acquired characters

Darwin thought it legitimate to postulate particles, the "gemmules," which carry such characters. Spencer thought all functions of the organism must be represented by "physiological units" of the protoplasm. Haeckel explained assimilation as the "perigenesis of plastidules." Weismann brought this method of attack to its climax in his complex series of assumed biophores, determinants, ids, and idants; though perhaps Heidenhain's graded series of life units, including super- as well as subcellular grades, has outdone that of Weismann. The cytologist has been unable to discover in the viscous semi-liquid, semi-solid colloidal mass of the cell any adequate evidence of the existence of such a particulate structure.

What seems to me the most important advance in our knowledge of cell architecture has been in the direction of the recognition of localized spatially differentiated regions of the cell body in which certain processes occur. To illustrate this point we may take the case of our increasing knowledge of the elaioplasts. Bodies associated with the appearance of oil in the cells have long been known in certain tissues of Funkia and Ornithogalum. Wakker's work on the elaioplasts of Vanilla vastly increased the clearness of our conceptions as to these structures. In the cells of the vanilla plant the elaioplasts appear as quite definitely bounded, specifically organized regions in the cytoplasm. They show a reticulated stroma with more or less included oil which with specific treatments may be made to exude upon their surfaces. But they are not sharply bounded, and they are quite irregular in outline. In general they are not so liquid or so differentiated from their surroundings as to round up, and here again we have the evidence as in the case of the chloroplasts that the cell elements may be sufficiently viscous to maintain irregular outlines by virtue of their semi-solid condition. Beer has been able to recognize and has figured elaioplasts in many tissues in the Compositae.

Other scattering observations indicate that they are of widespread occurrence in connection with oil production in many families of plants, and yet no one would deny that fatty materials may appear in cells, especially in the liverworts and fungi and in animals, in the entire absence of any specially differentiated region of the cytoplasm for their formation. We get thus, as I conceive, a clear-cut notion of the modern cytologist's conception of protoplasmic structure. Oil may be formed anywhere in the cell. If the conditions are favorable for its production in large amounts, this production is likely to become localized and to bring with it marked regional transformations, so that we can even speak of such a region as an elaioplast or organ of the cell. If such conditions are permanent the organ is permanent, and by virtue of the extreme non-diffusibility of colloids and their tendency to form surface tension membranes, may be perpetuated even through long periods of inactivity.

Similarly the plastids are regions of the cell body in which carbohydrates are deposited in solid or semi-solid form as starch grains, to be later redissolved and transported throughout the cell and the tissue or organ and to more or less distant parts of the plant. That the plastid is to be regarded as a region of the protoplasmic complex rather than as a differentiated and definitely delimited body is shown with especial clearness in the case of those algae whose chloroplasts are of irregularly lobed or frayed-out outlines. The functions of the chloroplast in forming assimilation starch are strictly dependent on the presence in it of green chlorophyl, and cytologically the chloroplast is perhaps little more than an area of the cytoplasm impregnated or infiltrated with chlorophyl. The leucoplast is obviously less differentiated than the chloroplast. That in the marginal lobes of the chloroplast the green pigmentation seems frequently to pass over by an imperceptible shading off in color into the gray of the adjacent cytoplasm is an observation easy to make on many of these algae. Hydrodictyon is especially well suited to illustrate the relations of the starch-bearing region to the remainder of the protoplasmic mass. The earlier writers had attempted to recognize a zonal differentiation in the Hydrodictyon cell, and the inner green zone or plastid with its pyrenoids was described as being free from nuclei; but Timberlake's sections show that pyrenoids and nuclei are scattered through the whole thickness of the primordial utricle about the central vacuole. Presumptively at least the whole primordial utricle is infiltrated with chlorophyl in the mature cell. The appearance of the cells of the young and growing nets of Hydrodictyon is also very suggestive as to the nature of plastids and their delimitation. As my photographs show, and as has been noted before, the ends of the young cells are gray and free of green chlorophyl, the latter occupying a band-shaped and very vaguely delimited zone in the middle region of the cell. As the nets grow larger, however, the chlorophyl spreads toward the ends of the cells until they are uniformly green in color, the number of pyrenoids increases from one to several, and the appearances suggest not the growth of a specific body but the increase of materials concerned with starch formation, pyrenoids and chlorophyl, and their gradual spread throughout the whole primordial utricle. This spread and increase of the pyrenoids involves their division, but the chlorophyl apparently merely diffuses out into the adjacent colorless regions of the cytoplasm as it increases in amount. In *Botrydium*, for example, and in the higher plants the chloroplasts appear as quite sharply delimited bodies of definite form and outline which themselves, at least at certain stages, arise by division, though their transmission as such through the egg and pollen tube may still be regarded as in question. It has not been adequately shown in any case, however, that the plastid has a specific membrane of its own like the plasma membrane or that of the nucleus. It is, so far as the microscope shows, a green-pigmented, denser region of the cytoplasm—a group of elements of the polyphase colloidal cytoplasmic system. The absence of a specific membrane about the plastid is shown especially by the widely recognized occurrence of stroma starch.

Starch formation in the plant has been studied chemically much more than cytologically, and our various theories of light assimilation have been based very largely on the chemical study of chlorophyl and observations on the appearance and disappearance of starch grains in their relation to the income and outgo of CO_2 and O_2 in the cell or leaf. Timberlake's studies of the relation of the pyrenoids to starch formation in Hydrodictyon, in which he shows that each grain begins as a segment of a pyrenoid which undergoes a series of microscopically visible changes in becoming a starch grain, indicate that starch formation in these cases at least involves physical transformations of masses which can be studied with the microscope as the atomic molecular readjustments with which the chemist deals. The work of Lutman on Closterium and of McAllister on Anthoceros have added a further series of observations in the field of the cytology of metabolism which indicate that the microscope is to play an increasingly important rôle in the study of these problems which have hitherto seemed open only to the methods of chemical analysis. It may be of interest to note that while the most widely current chemical theories of light assimilation seem to favor a katalytic theory of carbohydrate formation, all these cytological data point just as clearly to the acceptance of a metabolic theory. What is known cytologically of leucoplasts and chromoplasts agrees equally well with the conception of the plastid as a region of the protoplasm specialized with reference to carbohydrate metabolism. The leucoplast without its starch grain or grains is, as noted above, apparently a very slightly differentiated body indeed. The loss of chlorophyl has left it with very little to distinguish it from the adjacent cytoplasm, and yet the layer about a large stratified grain of storage starch is the seat of highly characteristic chemical transformations which, as Denniston's studies show, involve the formation of a cytologically demonstrable differentiated zone between the plastid and the stratified portion of the grain.

If Schimper is correct that the chromoplasts are derived from the other plastids by chemical transformations, we have in the frequently crystalline appearance of the latter the evidence that here again the plastid in the older tissue cells is a region in which the deposit of pigment crystals takes place.

The carbohydrate-forming plastids have gained a greater degree of permanency in the cell than the elaioplasts, so far as we know them now, and it is of the greatest significance that, associated with the growth and division of the cell, they so regularly arise by division. This division is a simple constriction both in the case of the plastids and of the pyrenoids. It is clear that pyrenoids may arise *de novo* in the cytoplasm. Timberlake could not convince himself that they certainly persist through swarmspore formation in Hydrodictyon, and Gilbert Smith has recently shown that they certainly arise *de novo* in three of the four cells produced by the double division of a mother cell in Scenedesmus and certain other algae. As to the chloroplasts, as noted, Schimper's evidence of their persistence through the egg stage, though his figures are clear enough for Daphne and Hyacinthus, cannot be regarded to-day as completely convincing in spite of the *quasi* support his theories have received from the theory of the mitochondrial origin of all plastids. In such forms as Hydrodictyon the division of the chlorophyl-bearing plasm is the division of the primordial utricle itself, but in the division of the tissue cells of the higher plants the independent constriction and bipartition of the plastid as such is to be reckoned with as a cytological fact of the first significance, and we must simply confess that we know nothing of the fundamental physical-chemical processes by which such constrictions are initiated and carried through. Our increasing knowledge of the chemistry of the carbohydrate and protein molecules has given us no clue to the solution of the problem of division, whether in the case of the simple bipartitions of these plastids or the complex mechanical processes involved in karyo- and cytokinesis. Under such circumstances, however, it is worse than useless to use such phrases as "tendency of protoplasm to divide" or "tendency of living materials to reproduce by bipartition." The problem is to be attacked, as it seems to me, from the standpoint of the newer evidence and conceptions as to the physical conditions existing in polyphase and compound colloidal systems rather than from that of a study of the chemical organization of the protein molecule.

Our knowledge of the visible structures concerned with oil and carbohydrate formation in the cell, as well as our knowledge of the sources of the materials and the possible chemical stages in the synthesis of starch from CO_2 and H_2O, give us a standpoint from which to obtain suggestions as to the organization of protoplasm and indicate the progressive localization of these processes in the protoplasmic mass with the formation of more and more definitely differentiated organs which finally reproduce by division.

In sharpest contrast with these contributions of cytology to our knowledge of oil and carbohydrate formation in the cells, I would set much of the modern literature of the chondriosomes, mitochondria, etc. Here, it seems to me, instead of a critical study of protoplasmic structure in relation to cell functions, we have in too many cases a mere reactionary movement taking its origin in the old view that we should hope to find in the cell the physical embodiments of the gemmules, pangens, ids, plastidules, etc., of a generation past. In so far as Meves, Duesberg, and others have endeavored to associate the formation of muscle rods, nerve fibrillae, etc., with visible elements of the embryonic cytoplasm, their work is, of course, highly suggestive and stimulating. I do not wish now to attempt to pronounce a judgment on the evidence as given by the authors noted above as to the relation of so-called chondriosomes, mitochondria, etc., to the processes of cellular differentiation in animal tissues. Their figures are in some degree at least convincing, and if confirmed will, in my opinion, mark one of the longest forward steps that have yet been taken in our investigation of the physical basis of life and life processes. Much less satisfactory is the evidence of Regaud, Dubreuil, and others who attempt to associate the chondriosomes with fat-formation, cell secretion, etc. If muscle rods, nerve fibrillae, etc., are actually formed out of unit semi-solid elements already existing in the cytoplasm of the embryonic cells, it certainly strengthens greatly what we may call a physical-mechanical, as contrasted with a chemical, viewpoint as to life processes. The visible structure of the protoplasm is not then, as Lundegårdh would say, the expression of the chemical transformations going on at the moment, but something vastly more permanent and mechanical. It should be regarded as a physical system of relatively permanent unit elements in definite space relations to each other and undergoing more or less progressive and cyclic rearrangements with resulting new and specialized capacities and functions. No more necessary investigations lie before us in cytology than those bearing on the question as to the histogenesis of such complex tissues as muscle and nerve fibers.

In the case of the attempts of Guilliermond and others to trace plastids, anthocyan vacuoles, metachromatic granules, pyrenoids, and other structures of the adult differentiated plant cell to cytoplasmic chondriosomes of the embryonic cells, the situation is clearer, if not so promising of illuminating new results. In a word, it seems to me that none of the evidence so far adduced as to a specific genetic relationship between chondriosomes and plant plastids is in any way adequate. It is not only that there is something like an equivalence in the weight of testimony in the literature on both sides of the question, but none of the evidence either pro or con seems to me to rest on adequately checked-up and convincing data of observation. That granules, rods, strands, etc., can be observed in the cytoplasm is undoubted and has long been known. The claim that those taking a given stain after a given fixation can all be classed together as coordinate unit elements, while suggestive, needs much further confirmatory proof like that which has been accumulated for the individuality and permanence of the chromosomes. That in certain cells the plastids can be recognized as very small cytoplasmic bodies with no starch in them was adequately established by Schimper, but that the plastid bodies necessarily and regularly arise from the chondriosomes it seems to me is by no means proved by such crude and diagrammatic figures and seriations as those so far presented.

In the present situation a somewhat sweeping criticism is, it seems to me, justified. I think we must all agree that the bulk of the literature of the plant chondriosome is a mere tabulation of the appearance of variously fixed and colored particles in the cell body with the hope that such bodies may later be found to be specific and fundamentally significant. I cannot attach great importance to the contention that such bodies, as a result of their locations in the cell, are distributed with approximate equality to the two daughter cells in division. The significance of such a distribution depends entirely on the specificity of the bodies and their relations to cell functions.

I have illustrated my viewpoint as to protoplasmic structure rather fully by the cases of the elaioplasts, plastids, and chondriosomes. The recent literature on these structures seems to me especially suggestive of the tendencies which are promising and of those which are reactionary in present-day cytological literature.

The conceptions of cytologists as to the chromosomes as units of cell structure are much more definitely fixed as a result of the vastly greater amount of attention which has been devoted to them. It is of interest to note that cytologists have devoted their attention almost entirely to the phenomena of reproduction and heredity. The phenomena of direct and indirect nuclear and cell division in asexual reproduction on the one hand, and of chromosome reduction and nuclear and cell fusion in connection with sexual reproduction on the other, have furnished such a wealth of easily accessible data that the processes of cell metabolism, growth, and irritability have been relatively neglected.

In the same way those physiologists who have used principally the methods of chemical analysis and physical measurements have found just these problems which the cytologist has neglected the more accessible. There has grown up thus an interesting division of the field according to the methods of study used by the investigator into cellular physiology or cytology, dealing largely with reproduction, and what is generally known as plant physiology, dealing quite as exclusively with metabolism, growth, and irritability. This might seem to indicate that the physiology of reproduction is a negligible field. At least one recent text-book of plant physiology states that the subject of reproduction has been adequately treated under the head of morphology. Such vagaries of viewpoint and opinion may safely be left to the future for correction, but it is the conspicuous fact that cytologists have largely concentrated their attention upon the phenomena of reproduction with the result that unquestionably the chromosomes are the best known bodies of their size in the whole field of science. The attempt to question the validity of the evidence for the existence of these structures in the living cell and to class them and other cell structures as products of fixation, staining, etc., has broken down completely. The older studies of Strasburger on division figures in living cells have been confirmed and extended by Lundegårdh and others. The essential characteristics of the chromosomes as to their form, size, and position in the cell and with reference to each other are recognizable in cells that are still alive and going through the processes of division. Their persistence in the resting condition of the cell in many plants either quite unchanged or as the so-called prochromosomes has been adequately demonstrated in fixed and stained material by Rosenberg, Overton, and others. Leaving aside the doubtful cases of the bacteria, blue green algae, and perhaps some protozoa, it is well nigh universally agreed that every cell has its specific complement of chromosomes quite definite in number, size, and perhaps in relative position in the cell body.

Further, they reproduce only by the division of parent chromosomes—a division which again outside the cases of certain protozoans gives evidence of its painstakingly equational character. We have then in the chromosomes subsidiary bodies in the protoplasm which duplicate in their permanence and method of reproduction the cell itself. As Boveri has emphasized, each chromosome has a life history of its own. It divides for reproduction, and each daughter chromosome grows to the size of the parent chromosome and in cyclic fashion is again divided. This is the basis for the doctrine of the individuality of the chromosome and has been used in support of the much vaguer, panmeristic doctrines of cell division and of the older theories that the cell is a complex of lesser life units, each, however, endowed with the full complement of the essential cell characters—the capacity to assimilate, grow, and divide cyclically into equivalent daughter units. These latter conclusions, however, it seems to me far outrun the facts. The data from elaioplasts, plastids, vacuoles, nucleoles, etc., suggest that, while permanence and reproduction by division can be present in various degrees in all these structures, they are rather acquired conditions worked out and developed in connection with the metabolism of the cell as a whole than essential characteristics of life units which by their combination then make the assimilation, growth, and division of the cell as a whole possible.

The permanence and equational division of the chromosomes are none the less the great outstanding discoveries of cytology as to cell organization, and here, as in the case of the constriction of the plastids, the underlying physical and chemical phenomena involved have so far escaped discovery. Neither chemistry nor physics furnish any data which aid the cytologist to discover why the segments of the spireme thread should split longitudinally or why the spireme should divide transversely to form the chromosomes. For the separation of the daughter chromosomes we have the possibility of contractility in the spindle fibers, protoplasmic streaming even, etc.—processes with adequate physical analogies—but the initial splitting of the chromosomes before the spindle is formed is quite without parallel in the behavior of atoms, molecules, or larger colloidal particles as known to the chemist and physicist. The division of plastids, chromosomes, and, as we shall note presently, centrosomes, as well as the pairing of chromosomes in cell and nuclear fusion, are basic data of cytology that so far differentiate cellular organization and processes from those of unorganized matter.

As to the functions of the chromosomes, we have a mass of evidence, which has been so many times and so well summarized that I need not rehearse it here, that they in some way provide for the so-called transmission of the hereditary characters. The evidence that the chromosomes are a physical basis for heredity is, it seems to me, entirely convincing and adequate. It is particularly significant that with the intensive study of heredity which began with the Mendelian revival nothing has been discovered which in any essential way invalidates the evidence from cytology that at least certain hereditary characters are in some way transmitted through the chromosomes. Indeed, the parallelism between the processes involved in chromosome reduction as described by cytologists and the theoretically postulated behavior of factors in segregation is regarded as one of the strong points in favor of the whole Mendelian theory.

On the other hand, when we touch the question as to just how the chromosomes function in heredity, and more definitely how the qualities of the tissues and organs and of the organism as a whole which are borne by them come to expression in the morphogenesis both of the embryo and the adult, we find ourselves again at an *impasse*. It is easy to say that the serration of a leaf edge is an inherited character transmitted by the chromosomes of any parent plant which possesses it, and the statement harmonizes with practically all known data of cytology and experimental genetics, but to attempt to give this generalized formula of concepts concrete reality by telling how the serration is represented in the chromosome and how it comes to expression in the many-celled leaf is quite beyond us as yet. It is quite possible that we are astray in our conception of representation on the one hand and the characters of many-celled organs on the other. At any rate, the method of functioning of the chromosomes in heredity is a problem of the future, though we can have no doubt that they are just as definitely related to hereditary transmission, whatever that implies, as are the plastids to carbohydrate metabolism.

From the standpoint of our question as to the structure of protoplasm, I think we may say that the chromosomes are each regions or portions of the protoplasm which by reason of the localization and specialization of certain functions and processes in them have come in some degree as has the cell itself to have a permanent unity and identity, and to arise only by division of parent chromosomes. The protoplasm is not an aggregate of such bodies, but its activities have been specialized and localized till such bodies as chromosomes have resulted. As a polyphase colloidal system it has furnished the internal condition for the development of the greater and greater differentiation, specificity, and fixity of its phases.

The centrosome or central body with its obvious relation to cell dynamics in the division both of nucleus and cytoplasm, and with its more recently discovered relation to cell movements as the blepharoplast, with its frequently, if not always, minute size and resemblance to other granules or groups of granules in the protoplasm, has been a main support for all theories of cell structure involving the idea of living granules of ultramicroscopic or at least sub-cellular size. Heidenhain makes it the type of one of his grades of life units. The evidence that the granules (centrioles) or groups of granules (microcentra) regularly arise by division of parent granules or groups in nuclear division in animals and lower plants is convincing, and yet in Bryophytes, Pteridophytes, and Cycads whose nuclei divide without the presence of centrosomes they appear apparently *de novo* as blepharoplasts in the formation of the motile male cells and even in the last few preceding nuclear divisions. Such evidence as this is most convincing, as it seems to me, as to the close interrelations of structure and function in protoplasmic organization. I have developed elsewhere the idea of the central body as a region of connection between nucleus and cytoplasm and for the formation of fibrillar kinoplasm in connection with my studies of free cell formation in the ascus. The data as to the behavior of the central body in the mildews may be taken as embodying the idea of a cell organ which I am here presenting. The central body is a permanent structure in the mildew cell. I have been able to trace it at all stages of their growth and development both sexual and asexual. The central bodies arise only by division and when the nuclei fuse the central bodies fuse, and yet it seems to me this is no ground for regarding them as life units, individuals, in the full sense in which the cell is such a unit; much less for regarding the cell structure as an aggregate of such living units. The position and relation of the central body to the nucleus and cytoplasm in free cell formation give the best evidence as to its nature. It is, as noted, a region of the cell at which the chromatin of the nucleus and the cytoplasm come into specific relations by contact and where fibrillar kinoplasm is formed and passes out to form the plasma membrane of the young daughter cell, the ascospore. That a granule of some specific chemical compound could play such a rôle it seems to me is by no means so easy an assumption as that in this particular region where the nucleus and cytoplasm are so definitely connected we have a concentration, a localization, of formative processes which results in the production of the disc-like central body and the radiating fibrils which ultimately form the plasma membrane of the ascospore. The activity of the processes dies down after cell division is complete but increases again when a spindle is to be formed for the next nuclear division.

From this point of view it is quite conceivable that, as in the ferns and cycads, a central body should appear *de novo* at the poles of the spindles in the androgones, where fibrillar kinoplasm aggregates, and persist later as the region from which the fibrillar cilia arise in the metamorphosis of the androcyte into the motile antherozoid.

I have avoided introducing in this connection the still too vague conceptions of intracellular enzymes and their role in cell activities; but the processes of free cell formation in the ascus can certainly be well conceived as involving a fermentative katalytic action of the contents of the nucleus on the adjacent cytoplasm in the region of the central body which results in the diffusion outward from the center of the material of the radiating fibrils.

The central body in its obvious dynamic relations to the other structures of the cell illustrates especially well the conception of cell structure which implies differentiated regions of a colloidal system in which special processes have become localized and tend to remain fixed. I have endeavored in my discussion of the conceptions of the cytologist as to cell structure to present them as far as possible from the standpoint of our present conceptions of the protoplasm as a polyphase colloidal system or complex of such systems. We may turn now to the more specific discussion of the influence which the new discoveries in the chemistry of the colloidal condition has had on our conception of cell structure.

DATA FROM THE CHEMISTRY OF THE COLLOIDAL CONDITION

The contributions arising from the modern study of matter in the colloidal condition to our conceptions of protoplasm have been, in my opinion, of the most far-reaching significance. We can perhaps appreciate most fully the change in the relations of biology and chemistry which has come with the development of the chemistry of the colloids if we consider the contributions of chemistry to that oldest and most elusive of biological problems—the nature and origin of adaptive form. It is here perhaps in the problems of morphogenesis that chemistry has appeared most helpless and the biologist has felt most justified in resorting to mystical and vitalistic conceptions of regulative principles, developmental tendencies, etc. I have referred above to our inability to conceive how the chromosomes as bearers of the hereditary characters can control the development of the inherited form characters in ontogeny.

The attempt to explain the form of organisms on the basis of analogies with crystalline forms and configurations has failed so conspicuously that biologists might well perhaps feel justified in questioning the possibility of a chemical theory of plant and animal form. A glance at the older and the more recent attempts in this direction is perhaps of interest.

Grew in 1672 felt the necessity of attacking the problem of the causation of plant forms from the standpoint of the forms of the crystals of salts found in plant juices. Out of the few and simple crystal types which he could isolate he put together groups which were supposed to explain the development of the trunk, the divergence of branches from the main axis at various angles, the serration of leaf margins, the formation of spiral vessels, and, to Grew most important of all, the very method by which the "fibers" are spun together to form the cell walls in Dame Nature's endless weaving of the lace-like patterns of the plant tissues. This was in 1672 and dates the beginning of the cell theory. In 1903 Przibram, undeterred by the failures of three hundred years, again claims to lay the foundations of a true theory of morphogenesis by a comparison of form development in both plants and animals with the growth, twinning, regeneration, etc., of crystals. He compares the replacement of a broken-off angle of a crystal to the regeneration of a salamander's leg and the replacement of a leaf tip. The bifurcation of a fern frond looks to him like the twinning of a crystal.

Przibram's figures and ideas are perhaps not as crude as those of Grew, but the general consensus of biological opinion is, undoubtedly, that no progress has been made along these lines. Such viewpoints lead simply into a hopeless *cul de sac* and seem to make mockery of the whole attempt at a chemical explanation of life phenomena.

The change that came with the recognition of the colloidal condition as a phase of material existence comparable in significance to the crystalline condition, the solution condition, the gaseous condition, etc., was, as I have said, of the most far-reaching significance to the biologist. The formation of permanent or semi-permanent suspensions and the demonstration that conditions of equilibrium could be reached in such systems followed by the recognition and careful descriptive characterization of sols and gels as studied *in vitro* brought chemistry and cytology on a common ground. One of the most important results of the study of the colloidal condition is the recognition of the fact that the units in colloidal systems, especially those of proteids, carbohydrates, etc., are large enough to be distinguishable at least with our present microscopes.

With the recognition that semi-fluid systems in physical-chemical equilibrium can be constituted of units larger than the molecules and within range of study at least with the ultra microscope, the possibility of assuming a complex meta-microscopic organization of the protoplasm in which the essentials of vital processes are carried on is made less plausible. These foam and emulsion structures are the first and most obvious characteristics of protoplasm which the microscope reveals. Even more, the evidence that in this colloidal condition the transition from liquid to solid, from sol to gel, tends especially to pass into an indefinite series of gradations gave a basis for the explanation of that mixture of the properties of solids and liquids which has puzzled students of protoplasm. In the light of the effects of temperature changes on the phases of a colloidal system the familiar biological phenomena of heat rigor, *rigor mortis*, protoplasmic coagulation, etc., could be at least paralleled by phenomena *in vitro*. The reversibility of the processes in certain cases and their irreversibility in others also parallel other familiar cytological data.

The biologist could only demur when the chemist demanded that he describe the phenomena of plant form in terms of crystallography and the processes of nuclear and cell division in terms of the chemical reactions of substances in solution. But Rhumbler has made real progress in describing the form of the shells of Foraminifera in terms of surface tensions in an anomogenous semi-liquid system, that is, a system whose liquidity varies in its different parts so that the homologous surface tension angles are always equal though non-homologous angles may be widely different. To say that the chromosomes go into solution in the telophases and reappear as crystals in the prophases was palpably absurd, but to describe the change as the passage of a gel into the continuous phase of a sol and its reverse is a chemical equivalent for many descriptions of the breaking up of the chromosomes in the telophases and their reconstitution in the prophases as found in current cytological literature.

The concrete data of the chemistry of the colloidal state so far relate chiefly to simple two-phase systems, and the conditions of the two phases are conceived as a more and a less watery phase of a single compound, though there is nothing in the conception of a sol to suggest such a limitation. Little has been done, too, toward the analysis of those intermediate conditions between the sol and the gel, though it is perhaps just here that the bulk of cytological phenomena belong. Still, there are those who on the meager data already available have formulated theories of protoplasmic structure in terms of colloidal systems.

To present a picture of the present chemical theories of protoplasm we must recognize two quite divergent tendencies or schools of thought which are largely represented amongst biologists and chemists of the day. First, the group of which we may take Verworn as a representative, who hold that a single very complex chemical compound, for Verworn the biogen, built up on the benzol ring and with Ehrlich side chains for dissociation and restitution, is the essential physical basis of life. The other visible constituents of the cell are to be regarded as more or less accessory. Life is the dissociation and restitution of biogens; all else is secondary.

The second school, which we may represent by Hofmeister, holds that the protoplasm is essentially an aggregate of compounds of varying complexity. Hofmeister takes at once the conception of a polyphase colloidal system as the basis of his account of cell organization.

The theory of a single living substance passes easily into the conception of specific chemical substances for each species of organism as developed by Kossel and carried still further by Correns in his theory of self- and cross-sterility and -fertility as due to similarity and dissimilarity of the specific individual substances in the same or different individuals. Correns has developed the interesting criticism of the doctrine of individual stuffs that even if the possible number of stereoisomers of a carbohydrate with 40 carbon atoms in its molecule was as great as 2^{40}, about a billion stereoisomers, there still would not be enough to provide a different one for each rye plant, for example, since a single crop of rye in Europe amounts to 41 billion individual rye plants. Reichert would have the genus, species, variety, race, sex, individual, and even tissue or organ stuffs the countless stereoisomers which the complexity of the protein molecule makes possible.

The theories which postulate a single living substance have been developed by many into a doctrine of protoplasmic structure as a simple, even a two-phased system. Bütschli's foam or alveolar theory would find the essential substance in the continuous phase while the contents of the alveolae, the disperse phase, is simply a watery cell sap. Various granular inclusions in the continuous phase are also assumed. Beijerinck and

Lepeschkin and all adherents of the so-called granular theories would make the disperse phase, consisting of the discrete particles, the bioplasts of Altmann, the plasomes of Wiesner, the chondra of Rohde, and, in general, the microsomes of older authors, the real living material units, while they would hold the continuous phase, their hyaloplasm or interstitial jelly, as dead or unorganized, perhaps a secretion of the granules. If Bütschli's theory is correct, the protoplasm would be a foam. If Beijerinck's and Lepeschkin's theory is right it would perhaps be better called an emulsion, using the terms to distinguish the relative importance of the disperse and continuous phases.

The crude simplicity and general inadequacy of these latter conceptions and the bitterness of the controversies which have been waged over them, especially by Bütschli and his followers, have done much to bring the whole subject of protoplasmic organization into disrepute. On the other hand the conception of protoplasm as an aggregate of complex compounds, a polyphase colloidal system or system of systems, seems to do much more adequate justice to the observed facts. The sols as at present commonly described permit only a single continuous phase, though the discontinuous phase might consist of an indefinite number of discrete bodies homogeneously distributed or even with zonation or other localization of certain elements according to their chemical and physical interrelations. But substances of greater viscosity may separate out as reticula and give us thus several continuous or partially continuous phases. The existence of such interlacing strands and films is a familiar fact of protoplasmic structure in the killed and fixed condition, and can also be observed in living pollen mother cells, spores, etc. Frommann's familiar figures of the protoplasm in the end cells of glandular hairs suggest such structures.

Hofmeister emphasizes the importance of the surface tension membranes between the different substances in the cell which are due to their immiscibility as furnishing just the means necessary to hinder diffusion between the different regions of the cell and to make possible the maintenance of the various structures and organs of the cell which the microscope reveals. This immiscibility of the different assumed substances makes possible also the different functions of the various cell parts, functions, as he points out, involving the simultaneous occurrence in different parts of the cell of different and frequently opposite chemical transformations such as hydration and dehydration, oxidation and reduction, synthesis and decomposition. The decomposition of glycocoll to urea presupposes a specific seriation of the reactions involved which implies an independent activity of the various intermediary substances produced such as could not exist if the protoplasm were a homogeneous mixture. The possibility of such reactions presupposes, for Hofmeister, a so-called chemical organization of the cell. The endless series of ferments and their products are thus separated and enabled to carry out their independent acceleratory reactions by virtue of the interfaces formed between them as phases of a colloidal system. The slowness of the diffusion of colloidal ferments leads to their becoming rooted as it were in certain regions of the cell most favorable for their activity.

No one can deny that this picture of the chemical organization of the cell does full justice to many of the observed facts of cytology as well as to the processes of physiological chemistry. The conception of the enzyme is perhaps over-emphasized in view of the slight knowledge which we have of the chemical nature of these elusive compounds. But the localization of functions in the cell and the special acceleration of certain general reactions in particular regions of the cell are conceptions which can be connected directly with the cytology of starch formation, oil formation, the building of astral rays, spindle fibres, and cilia, the production of cell pigments, etc. Hofmeister does not at all emphasize the phase relations of these various constituents of the cell, and it is obvious that a polyphase colloidal system does not of itself involve such structural differentiations as Hofmeister assumes and the microscope reveals. No matter how great the number of phases or how intimate their interrelations are assumed to be, the polyphase system in itself might be in general homogeneous throughout its whole extent, that is, the particular phases and their interrelations might repeat themselves in all directions through the mass in a uniform and undifferentiated sequence. That is, just as in a two-phase system any one unit area large enough to include the two phases will be essentially like any other unit area of equal size in the mass, so in the polyphase system the mass is naturally conceived as including an indefinite number of repetitions of unit areas essentially alike as to their makeup. The polyphase system is merely the two-phase system increased as to the number of its constituent elements. It is only by adding the conceptions of zonation and other types of segregation of the elements of the polyphase system due to their chemical interrelations that we arrive at a parallelism with what is seen in the cell.

We can put this in another way which will at once bring out the peculiarities of cell organization as compared with polyphase systems *in vitro* by noting that the polyphase system may be homogeneous in the respect that it shows no axial differentiation. Whatever the interrelations of the phases as to internal and external, sol or gel, they will be the same at the top as at the bottom, in the front as at the rear, on the right side as on the left side. The only exception is that any polyphase system will differ on its surface as compared with its interior, that is, will show some concentric zonation. This difference has been exploited to the full in the numerous recent attempts to utilize the data of colloid chemistry in the analysis of the structure and functions of the plasma membrane. It would take us too far afield to review the data in this complicated subject further than to note that none of the theories—lipoid, mosaic, adsorption, filter, etc., have contributed anything very positive to the general theories of protoplasmic structure.

Aside from this concentricity there is no evidence of symmetry relations or polarity in a polyphase colloidal system as such. On the other hand, polarity is one of the most obviously demonstrable characteristics of cell organization. Polarity in herbaceous and woody shoots is known to all. That the polarity of the shoot as a whole is due to the polarity of the individual cells has been made highly probable by appropriate experiments. That polarity is also a property of cells of simpler plants and doubtless of all cells is shown by Tobler's elaborate and far-reaching demonstrations for algal cells.

The simplest possible statement of the facts as to polarity in the cell brings out at once the conspicuous differences between cell organization and that of a polyphase colloidal system as such. Greil, who is perhaps the latest to attack the problem from a theoretic standpoint, in his labored effort to bring all morphogenetic factors into an epigenetic rubric can get no further with the polarity of the animal egg than to say that it would be very remarkable if with such long-continued and mighty growth of the yolk-containing egg cell an entirely homogeneous consistency, tectonic, of the cell organization should be maintained. Polarity is for Greil simply a matter o eccentricity in the deposit of accumulated reserve materials, and yet this simple statement of its eccentricity at once differentiates the telolecithal yolk-bearing egg from a polyphase colloidal system as such. Greil quite ignores the fact that Tobler has shown the existence of pronounced polarity in algal cells which contain little or no reserve foodstuffs and that it has never been possible satisfactorily to associate the polarity of shoots, etc., of the higher plants with any special distribution of either "formative" or reserve stuffs.

Greil goes so far as to say that the egg furnishes only bilateral polarity as a form-determining factor in the development of the embryo. This standpoint implies a program rather than present achievement, but it is interesting to us as showing what stress a confirmed epigeneticist like Greil lays on polarity as a characteristic of cell organization. To say that the egg furnishes only bilateral polarity as a form-determining factor implies that it will be possible to show how the bilateral polarity of the different species of eggs varies, since many eggs show bilateral polarity and yet with similar environment the product of their development is very different.

It is not, of course, shown to be impossible that polarity may be in its essence simply the expression of the two-sided or bipolar distribution of the visible structural elements of the cell such as the nucleus, centrosome, plastids, etc. It would seem *a priori* more probable that the eccentricity in the deposit of such metaplasmic inclusions as yolk, starch, fat, aleurone, etc., is the expression of a polarity in the more fundamental architecture of the cell rather than its cause. This is the sort of polarity shown in Rabl's classic figure which represents in my opinion the most adequate diagram of cell organization so far conceived. The swarmspores of an alga like Pediastrum with their plastids, mouth-piece, blepharoplasts, cilia, etc., are visibly highly polarized structures, and it will be of great interest to determine whether this visible polarity coincides with the major axes of the adult cell of Pediastrum and the apparent affinities which determine the orientation of each cell with reference to its fellows and to the form of the colony as a whole. This problem is by no means insoluble with the modern culture methods available for keeping such algae in large numbers under continuous observation.

That in Pediastrum the swarmspores show polarity in at least two axes and that this polarity determines their mutual interactions and final position in the colony is shown conclusively, as I have pointed out elsewhere, by the symmetrical organization of the colony and the method of its formation from a group of freely swimming cell units. Polarity exists in probably all the tissue cells of metaphytes and coenobic plants and in many protophytes. It is apparently independent of the uni- or multinucleated condition of the cell, which shows that it is in some cases at least a more generalized characteristic of the cell as a whole rather than a mere expression of the space relations of the nucleus and cytoplasm in a diagram like that of Rabl. Bilateral and radial symmetry are shown also in the cells of desmids, diatoms, and other protophytes, these latter showing in Rhumbler's term the anomogeneity of the protoplasm as a liquid. It is sufficiently clear, it seems to me, that in the presence of polarity and the various symmetry relations we have a fundamental distinction between cell organization and that of polyphase colloidal systems as they are commonly produced *in vitro.*

Furthermore, the outstanding fact not sufficiently recognized in the theory of colloids as at present developed is that we may have at least more or less differentiated colloidal systems within a colloidal system. The cell must at least be conceived as a complex of such colloidal systems, some possibly simple two-phase systems as perhaps a vacuolated nucleole, some polyphase as the nucleus taken as a whole within the cytoplasm. In such cases the interior system as a whole will show a tendency to form convex surfaces toward the enveloping system or systems. Perhaps the nearest approach to an experimental demonstration of such an organization is found in Hardy's development of the evidence for secondary interior phases. If a mixture of gelatine and water is cooled to a certain temperature, we obtain a watery interior phase in a continuum of denser gelatin; if now the cooling is continued small particles appear in the watery disperse phase which may make chains which anastomose to form reticula constituting a secondary interior gelatine-rich phase. In this case we should still have no polarity in the mass as a whole. The interior phases would be repeated equally in all directions throughout the whole system. None the less the experiments as described are highly suggestive as to the physical relations under which the internal structures of such a complex system as the nucleus exist. Such secondary interior phases doubtless exist in the case of the granular precipitates in vacuoles and the frequently observed inclusions in the nucleoli. They also provide for the development of filar and reticulated structures in colloidal systems in which the general consistency is still quite fluid. What appears perhaps most inadequate in the data of colloidal chemistry as a basis for the conceptions developed from a study of the cell itself is the failure of students of unorganized colloids to emphasize the evidence for the existence of the thready reticulated and filar structures which are so familiar to the cytologist in fixed material.

Boresch has also described filar structures in the living protoplasm of moss cells whose method of occurrence, sensitiveness to environment, reagents, etc., suggest their resemblance to the reticulated chains of granules produced by Hardy. As Lundegardh has pointed out, these figures of Boresch show many resemblances to the so-called myelin structures and are doubtless in some cases the same cell elements which have been variously described as mitochondria, *Chondriokonten*, etc. They are far less thread-like than the highly differentiated, clean-cut fibers of the asters, spindles, etc., of our fixed preparations, but are interesting as showing that thready structures as well as granules, foams, emulsions, etc., are to be reckoned with as constituents of protoplasm. These fibers of Boresch, as also the mitochondria, show no polar orientation except perhaps as they are more or less passively influenced by the karyokinetic figures in dividing cells. Their form cannot hence be ascribed to the operation of fields of force, magnetic polarities, etc., operating on the cell substances, as is so frequently claimed for the fibers of the karyokinetic figures.

To provide an adequate basis for understanding the observed facts of polarity, however, it seems to me that the conception of compound aggregate polyphase systems is more suggestive than these attempted analogies between the magnetic poles and their fields of force and the karyokinetic figures. The suspension of one or several polyphase systems within another polyphase system is entirely harmonious with what we know of the high viscosity of many of the constituents of protoplasm. In the spatial arrangement and interrelations of these systems polar differences of the most diversified types are bound to arise in the mass as a whole and express themselves in the form and relative rigidity and surface tension of different parts, as well as in the interrelations between the cells of a group in contact.

But the most important factor which the cytologist must recognize with reference to the development of such systems as are shown in the organization of the cell is the time element. In contrast with any known unorganized system, the cell propagates itself by division, as Weismann has so adequately and fully emphasized. This means that the protoplasmic structure is not formed *de novo* in reproduction, but has perpetuated itself as such from the remote geologic periods when life first appeared upon the earth. The spatial interrelations of the colloidal elements and systems of the cell are not, then, such as we might expect to duplicate by mixture *in vitro*. They are in some degree at least the product of the infinitely varied external and internal environmental changes to which the cell in its long evolutionary history has been exposed.

GENETICS AND THE STRUCTURE OF PROTOPLASM

It is perhaps unfair to the geneticists to consider the great contributions which they have made in recent years in the light of their bearing on current theories of protoplasmic structure. The adherents of the doctrine of unit factors assert repeatedly that they are quite unwilling to commit themselves as to the form in which these unit factors are to be conceived as existing in the germ plasm. We are told that they are merely presenting facts as to the behavior of visible characters in breeding experiments and that we may imagine any sort of representation of these factors in the germ plasm which we please. And yet views so widely held and so stimulating of research as the factorial hypotheses are certain to influence strongly at least our *a priori* conceptions of the structure of the germ plasm and of protoplasm in general.

The serial arrangement of such factors in the chromosomes seems to be involved in that parallelism between the data as to chromosome reduction and the segregation of factors which has afforded such strong support for the whole Mendelian theory. We may note in passing that Trow points out regarding the evidence of serial arrangement derived from linkage that the numerical data used as the basis of the assumption of a serial order of the factors constitute "a type of representation common to every set of phenomena which can be expressed as percentages."

Still, it may be noted further that if we are not to regard the chromosomes as so many chains of factorial beads there is no other hypothesis which has any recognized standing at present with either cytologists or geneticists. The development of the conception of the cell as a polyphase colloidal system seems to point in another direction, but it has led to no very definite ideas as to the way in which the characters of the adult many-celled organism are represented in the germ plasm. It is doubtless true, as is so strongly felt by the newer epigeneticists like Greil, that the idea of a representation of characters of a many-celled organism, especially those due to the inter-relations of the cells, in the chromosomes cloaks a vast amount of obscurity. These latter biogenetic characters must certainly be put in a different category from the characters which Detto has called *metidentical* and whose inheritance offers relatively little theoretic difficulty.

It is certainly worth while to consider most carefully these conceptions based on the facts of breeding from the viewpoint of their influence on theories of protoplasmic structure. The day is past for the explanation of vital phenomena by the assumption of units or particles endowed with properties which explain their assigned functions. Nowhere is the need of a critical consciousness of the whole protoplasm question shown more clearly than in the frequent looseness of such assumptions.

The assumption is that we can draw specific conclusions as to the constitution of the germ plasm from the behavior of visible characters in the multicellular organism, even though this behavior is so complex that it necessitates the assumption of several independent units in the germ plasm for one apparently individual character. Bateson's amoeba would have to be represented as of gigantic size in order to get points of origin for all the characters that have come out of it and been eliminated in evolution. There can be no question that with the intensive study of the past two decades the problems of heredity have been found to be vastly more complex than it was hoped they would appear when treated by the Mendelian method of analysis. The pangens of De Vries, at least in the earlier form of his theory, were regarded as relatively few in number and broadly pervasive in their visible effects in the organism. We are now apparently more inclined to Weismann's conception of indefinitely numerous determiners in more or less fixed space relations to each other.

The realization of the weakness of Mendelism in relation to facts as to the all-pervasiveness and interdependence of plant characters has led some of the defenders of the theory to assert that each unit factor may possibly influence every part of the mature plant.

The difficulty with all such assumptions of hereditary units of whatever kind is more fundamental. Take the case of the serrations of the leaf of the common nettle. Correns told us in 1903 that entire margins and serrate margins were due to a factor in the germ plasm for serratures paired with one for entire margin, and the whole was made an example of dominance and segregation. It is to be noted that Correns found teeth weakly developed in his recessives, and while so far as I am aware no one since has gone over the matter I am willing to predict on the basis of my studies on sugar and starch characters and aleurone color in corn that a whole series of intermediates between serrate and entire can be found and that a present day student instead of saying that there is one factor for toothed margin would say there are several or perhaps even twenty.

If serrateness and entirety were found to be absolutely hard and fast categories, units in behavior, there might be something in favor of assuming as a working hypothesis that each was represented by an equally hard and fast, definitely limited section of a chromosome. But if there are all degrees of variation from entire to deeply serrate, the existence of a series of units in the germ plasm, one for each depth of serrateness, is not obviously suggested. The series of fluctuating variants has a unity to the human mind quite as natural as any one of the particular grades of serrateness. This is evidently felt vaguely by those who assume modifying factors and factors of fluctuating potency. To assume, however, that we have explained anything or in any way contributed to clear up our knowledge of germ plasm or heredity by saying that the fluctuating behavior of the visible characters is explained by modifying factors in the germ plasm is a preformationism which would have put even Bonnet to the blush. My point is here that at every step the possibilities of the structure of the germ plasm as well as the visible behavior of characters must be kept in mind.

Perhaps the most obvious weakness of all these theories of units of protoplasmic structure and unit factors in heredity is that they carry in them the vices of the old preformationism. They seem too much like attempts to explain visible and familiar complexity by the assumption of a parallel complexity in the germ plasm, and this in spite of the generally admitted *incommensurability* of cell organization and metaphyte organization. Driesch, with all his tendency to mysticism, must be credited with having recognized and made clear that the facts of nuclear and cell division and the resulting perpetuation of the hereditary complex make it impossible to assume a spatial configuration of the germ plasm in three dimensions parallel to that of the many-celled organism as a whole. The theory of multiple unit factors attempts to maintain in lesser degree this same parallelism—with the added difficulty that the germ plasm which is to be equationally divided must even contain a number of unit factors for each character of the organism.

It is of interest to note in connection with these hypotheses of particulate structure in the protoplasm the available data as to the size of the various elements involved.

Human blood corpuscles	7,500	micro μ	
Anthrax bacillus	4,000–5,000	micro μ	
Cocci	500–1,000	micro μ	
Chromosome:			
Primula Kewensis with 18 chromosomes (Farmer)	1,262 × 1,110	micro μ	Vol. .8141 cubic μ
Primula Kewensis with 36 chromosomes (Farmer)	1,022 × 874	micro μ	Vol. .4088 cubic μ
Chromosome from macromere of Crepidula (Conklin)			Vol. 5.2 cubic μ
Chromosome from micromere of Crepidula (Conklin)			Vol. 2.6 cubic μ
Granules of central body (Marquette mss.)	300–500	micro μ	
Smallest gold particles observed in hydrosols	6–15	micro μ	
The same in non-permanent suspensions	75–200	micro μ	
Molecule of soluble starch (Lobry de Bruyn)	5.	micro μ	
Haemoglobin molecule	2.5	micro μ	
Casein molecule	2.4	micro μ	
Chloroform molecule (Jäger)	0.8	micro μ	
Alcohol molecule	0.5	micro μ	
Hydrogen molecule (O. E. Meyer)	0.1	micro μ	

The granules of the central body which relate themselves so conspicuously to spindle formation are perhaps of the same order of magnitude as some very small chromosomes, and a Micrococcus with all the characters necessary for growth, life history, and reproduction is again of about the same size.

Our positive knowledge of the size of both protein and carbohydrate molecules is very limited, but the figures given indicate that for example the linear dimensions of the chromosomes of the ordinary form of *Primula Kewensis* are some hundreds of times those of the molecules of starch and haemoglobin. There is ample space in these chromosomes for a number of molecules equal to the most extreme demands of the factorial hypotheses if each factor can be represented by a single molecule or even a group of molecules. These particular chromosomes too are by no means large. I have chosen them as illustrations because Farmer and Conklin respectively seem to have measured them with unusual care.

It is sometimes suggested that a factor may be embodied in a single molecule or by a mass of a single compound. It seems probable that colors and similar metidentical characters are due to single compounds or mixtures of a few compounds in the cells of the metaphyte body. That however the complex of cellular interactions including the regulation of the order and relative number of a whole series of cell divisions such as are involved in producing the serratures on the margin of a leaf can be represented by a molecule or group of molecules in a chromosome is hard to conceive. It would seem more natural to regard such organic regulations as the expression of the capacities for interaction of the complex cell mechanism as a living unit in its entirety. The delicately balanced and adjusted 1–5–10 relation between the cells of a bilaterally symmetrical sixteen-celled colony of *Pediastrum Boryanum* seem to be achieved by the interactions of the swarmspores acting as independent units each with a definite polarized organization and capacity to respond to delicate contact and pressure stimuli.

In any case we need more evidence as to the size of protein molecules before comparisons of the size of molecules and chromosomes can have much significance. Of more importance at present is the well-established evidence of specific mass relations between the various parts of the cell unit as a whole considered as a polyphase system, though here again the significance of the facts in their relation to the problem of protoplasmic organization is not yet clear. Strasburger had shown in 1893 that there is a tendency in young meristematic plant cells to the maintenance of a constant volume relation between the nucleus and the cytoplasm, the ratio of nuclear diameter to cell diameter being something like 2:3.

Gerassimow in his classic discoveries of methods for producing and culturing binucleated cells in Spirogyra and other members of the Conjugatae established experimentally the existence of a nucleo-cytoplasmic relation of mass in these forms, as have R. Hertwig and Boveri for various animal types. Gerassimow's data, however, do not cover the problems of chromosome size and number, though it is safe enough to assume that his binucleated cells of Spirogyra contain twice the number of chromosomes found in the uninucleated cells.

Conklin finds that the actual size of the chromosomes in the macromeres and micromeres of Crepidula varies with the size of the nucleus in which they lie but in lesser degree. "The average volume of the chromosomes from the larger nuclei is 5.2 cubic μ and of those from the small nuclei about 2.6 cubic μ. While the volumes of the nuclei as a whole are to each other as about 5:1, the volumes of their individual chromosomes are to each other as 2:1. There is a tendency to constancy in chromosome size, and yet, "just as the size of the nucleus is connected with the volume of the cytoplasm in which it lies, so the size of the chromosomes is connected with the volume of the nucleus from which they come." There is a tendency to a constant chromosome-nucleus relation of mass just as there is a nucleo-cytoplasmic relation of mass.

If in embryological and later development there were a gradual reduction in the size of the nuclei, a corresponding reduction in the size of the chromosomes might be taken as evidence of a distribution of tissue determiners in the crude Weismannian sense, but while, as Conklin shows, there is no nuclear growth of 100 percent after each division there is a growth of five to nine per cent in the volume of the nucleus with each division during early cleavage and a growth of one percent during later cleavage.

Of course these early divisions studied by Conklin and others relate to the development of the general symmetry relations and the *Anlagen* of systems and organs of the mature organism rather than to the production of the definitive *Anlagen* for the tissues. For plants at least the totipotence of the cells of the adult is evidence against the use of mass relations in the germ plasm at different stages of ontogeny as proof of its corpuscular constitution.

Meek's rather crude conception of a definite width increase in the chromosomes as we pass from the lower to more highly specialized organisms has apparently been refuted by Farmer's more careful measurements and analysis. Farmer finds that in *Primula Kewensis* the size of the nucleus varies with the number of chromosomes which go to make it up rather than with the total mass of the chromatic material. As quoted in the table above, the form of *Primula Kewensis* with double the chromosome number of its parents has larger nuclei but the total mass of its chromatin is the same. The doubling of the chromosome number has been brought about by dividing each chromosome of the parent species into two equal chromosomes. The size of the nucleus is in some degree influenced by the number of chromosomes rather than by the mass of chromatin as such. As Boveri holds, the surface area of the chromosomes rather than their total mass appears to be significant in influencing the nucleo-cytoplasmic mass relation.

The measurements of the mass of the germ plasm at various stages of development of the individual so far as they have been carried do however show clearly some tendency to the maintenance of more or less definite mass relations between chromosomes, nucleus, and cytoplasm—that is to the maintenance of a sort of mass equilibrium between the parts of the polyphase cell system. The data as given would indicate a higher degree of mass constancy in the chromosomes than in the nucleus as a whole and in the nucleus than in the cell as a whole.

The rather cataclysmic features of the early embryonic periods of development do not obscure entirely the tendency to constancy in the organization of the cell as a whole. Such elements as cell polarity based on the space relations of nucleus, centrosome, and cytoplasmic mass, the relative shape and position of special masses of food reserves, etc., all tend to remain constant or to change by slow progressive transformations and modifications.

In eggs and macrospores overloaded with large masses of yolk or starch as temporary food reserves, the obvious tendency is to regain the balance between nucleus and cytoplasm normal for the cells of the given species in its adult form. A wider range of data in this whole field of the size relations of the various cell constituents is needed as a basis for the further development of the conception of the cell as a complex of colloidal systems.

Farmer's results on two series of fern varieties are not consistent as to the relation of chromosome number to cell size, though for the lady fern series Strasburger's ratio that the diameter of the nucleus is to that of the cell as 2:3 holds good. As Farmer notes, however, the small size and large number of chromosomes in the ferns make them unfavorable material for such studies.

The evidence is certainly clear that the polarity and the mass relations of the parts of the cell, chromosomes to nucleus, and nucleus to cytoplasm, are in some degree specific, as is also the tendency to return to the norm for these relations when they have been disturbed. The further development and refinement of these concepts is of much importance for our conceptions of cell organization and for the transition from the old viewpoint that protoplasm as a substance has a specific structure to the conception that the fundamental organization of living material is expressed in the structure of the cell.

The attempts to recognize plasmodia, coenocytes, syncytia, etc., as protoplasmic rather than cellular are, it seems to me, superficial and misleading. The old attempts to solve the problem of protoplasmic behavior by the assumption that it is composed of physiological units, biophores, determiners, plasomes, pangens, etc., and the newer conception that its essential elements are unit factors, are, it seems to me, being merged in the conception that the structure of protoplasm is the structure of the cell as an organized system and itself the unit in all the complex interactions by which the egg develops into the specialized and differentiated many-celled organism.